



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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OCT 23 2003

By Certified Mail – Return Receipt Requested
And Facsimile Transmission

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448
CBER-04-001

Warning Letter

Ben R. Thebaut, M.D.
3401 PGA Boulevard, Suite 500
Palm Beach Gardens, Florida 33410

Dear Dr. Thebaut:

This letter describes the results of a Food and Drug Administration (FDA) inspection that ended on June 26, 2003. FDA investigators Ana del P. Cintron and Sherbert L. Samuels reviewed your activities as a clinical investigator for testing an investigational

[REDACTED] FDA conducted the inspection under the Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational drugs.

Based on the inspection, we have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 312 (available at <http://www.access.gpo.gov/nara/cfr/index.html>). The violations were listed on the Form FDA 483 presented to you at the close of the inspection.

We have reviewed your July 14, 2003 response to the Form FDA 483. Your response does not adequately detail corrective actions to ensure that the violations cited in the Form FDA 483 have been addressed. Significant violations cited during the inspection and our comments on your response are provided below. The applicable provisions of the CFR are cited for each violation listed below.

1. **You failed to obtain informed consent from study subjects in accordance with the provisions of 21 CFR Part 50 and the investigational plan. [21 CFR § 312.60].**

Protocol section 4.4.1 requires that potential study subjects must sign the written informed consent form prior to the initiation of the Preoperative Screening assessments.

Six potential study subjects [REDACTED] and [REDACTED] underwent Preoperative Screening assessment tests prior to signing the informed consent form as listed below:

Subject	Screening Assessment Test and Date	Date of Informed Consent
		9/1/99
		5/19/00
		6/14/00
		7/14/00
		8/24/00
		8/15/00

Your response letter acknowledges that the consent forms should have been signed prior to conducting the screening tests. In your response to this letter, please explain the corrective actions that have been or will be implemented to prevent a future recurrence.

2. **You failed to assure Institutional Review Board (IRB) review of the clinical study by not promptly reporting serious adverse events and deaths as required by the IRB. [21 CFR § 312.66].**

The IRB approved your protocol by letter dated 4/29/99, and specifically required that you report, in writing "...serious adverse reactions to the IRB within 5 days of their occurrence." However, you did not make written reports of ten serious adverse events within five working days, as required by the IRB.

Subject	Adverse Event (AE)	AE Date	IRB Notified
	Hospitalization/Fractured Sternum	7/15/99	7/17/00
	Prolonged Hospitalization/Fever	9/22/99	7/17/00
	Hospitalization/Chest Pain	9/27/99	7/17/00
	Transurethral Resection of Prostate	10/5/99	7/17/00
	Prolonged Hospitalization and Disability/Cerebrovascular Accident	12/21/99	7/17/00
	Prolonged Hospitalization/Fluid Overload	2/5/00	7/17/00
	Death/Cardiac Arrest		7/17/00
	Prolonged Hospitalization/Cerebrovascular Accident	5/16/00	7/17/00
	Hospitalization/Wound Infection	8/16/00	10/26/00
	Death/Myocardial Infarction		10/26/00

In your response, you state that these events were discussed in person with the IRB at its quarterly meetings during the conduct of the study, and that the delay in providing written reports of the events was an administrative oversight that has

been corrected. You state that you have been retrained in the proper reporting procedures for adverse events.

In your written response to this letter, please provide documentation of standard operating procedures that have been or will be implemented to ensure the proper reporting of adverse events to the IRB. Please describe the nature of the retraining you received.

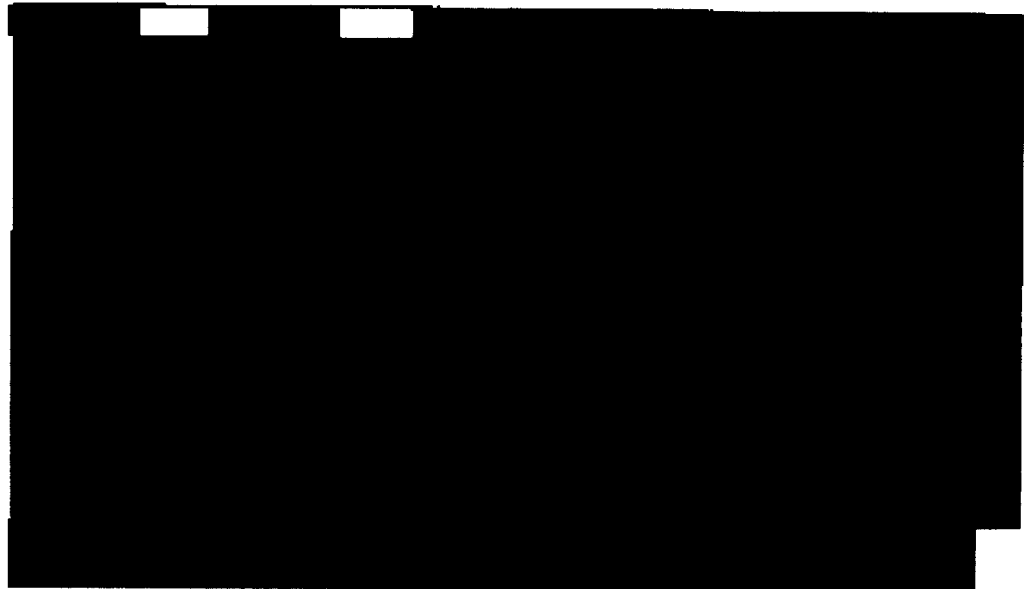
- 3. You failed to protect the rights, safety, and welfare of subjects under your care and you failed to ensure that the investigation was conducted according to the investigational plan and the signed investigator statement. [21 CFR § 312.60].**

- a. Protocol section 4.3.2.2 excluded subjects with [REDACTED]
[REDACTED] Subject [REDACTED] was not eligible to participate in the study
because this subject [REDACTED]
[REDACTED] during surgery, two days prior to the first [REDACTED] of the
investigational drug.

In your response, you state that this was discussed with the sponsor and that the [REDACTED] was not considered to be exclusionary for enrolling subject [REDACTED]. In support of your response, you cite a section of the protocol on page 49 called [REDACTED]. When we reviewed protocol [REDACTED] provided to the FDA, we were unable to locate a section entitled [REDACTED] on page 49 or elsewhere in the protocol. You acknowledge that in the future you will pay more attention to the specifics of the inclusion/exclusion criteria.

In your written response to this letter, please provide a copy of the section from Protocol [REDACTED] as cited in your letter. Please provide documentation that the sponsor prospectively approved the enrollment of subject [REDACTED]. Please also describe the specific actions you plan to take to prevent enrollment errors when conducting future studies.

- b. Numerous assessments were not completed as required by the protocol.
These included [REDACTED]
[REDACTED]
[REDACTED]
following examples are not a complete list.



In your response letter, you describe several reasons why the required study assessments were not performed, acknowledging that these were protocol deviations. You state that you held several training sessions with the staff throughout the conduct of the study, and that you now understand the need for better quality control throughout the conduct of clinical studies. All required assessments must be performed in accordance with the protocol.

4. You failed to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation. [21 CFR § 312.62(b)].

- a. Signed consent forms were not available for two prospective subjects [REDACTED] who were screened but not enrolled in the study. You wrote notes in the case report files stating that these informed consent documents were misplaced.

In your response, you state that the consent forms for the screen failures were not readily available at the time of the inspection. In your reply to this letter, please clarify whether these documents have been located.

- b. Source data for various assessments could not be located in the case report files or subject's medical charts.

In your response letter, you confirm that these source documents were not available at the time of the inspection. You indicate that you now

understand the importance of maintaining these records. In your reply to this letter, please clarify whether these documents have been located.

- c. Protocol section 9.3.2 requires that the clinical investigator retain the original signed consent form in the study files. The original consent forms could not be located for 18 of the [REDACTED] subjects enrolled in the study. Copies were available in study binders and subject charts [REDACTED]
[REDACTED]

We wish to comment on your responses to two observations listed on the Form FDA 483, Inspectional Observations. In regards to Observation 4B, you attribute the delay in your signature on the informed consent form to an “administrative oversight” that has been addressed in training. We wish to emphasize that your signature on the informed consent form documents that you were present when the risks and benefits of the study were discussed and when each prospective subject was given the opportunity to ask questions prior to agreeing to participate in the research. The fact that you did not sign the forms until long after the subjects signed suggests that you may not have been present when the informed consent was obtained. Please respond.

This letter is not intended to be an all-inclusive list of deficiencies. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations and to protect the rights, safety, and welfare of subjects under your care.

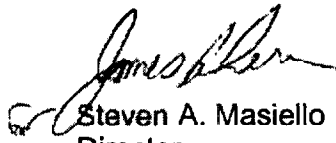
This Warning Letter is issued to you because of the numerous serious observations noted at the time of the FDA inspection. Please be advised that the failure to effectively put into practice corrective actions and/or the commission of other violations may warrant the initiation of enforcement actions without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs, and/or injunction.

You should notify this office, in writing, within fifteen (15) business days of receipt of this letter, of the specific actions you have taken to prevent the recurrence of similar violations in future studies. If corrective actions cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Please submit your written response with the requested documentation to:

Patricia E. Hasemann
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1448
Telephone: (301) 827-6337

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

Emma R. Singleton, District Director
Food and Drug Administration
555 Winderley Place, Suite 200
Maitland, Florida 32751

